Mechanisms of Improved Exercise Performance under Hyperoxia

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Abstract: BACKGROUND The impact of hyperoxia on exercise limitation is still incompletely understood. OBJECTIVES We investigated to which extent breathing hyperoxia enhances the exercise performance of healthy subjects and which physiologic mechanisms are involved. METHODS A total of 32 healthy volunteers (43 ± 15 years, 12 women) performed 4 bicycle exercise tests to exhaustion with ramp and constant-load protocols (at 75% of the maximal workload [Wmax] on FiO2 0.21) on separate occasions while breathing ambient (FiO2 0.21) or oxygen-enriched air (FiO2 0.50) in a random, blinded order. Workload, endurance, gas exchange, pulse oximetry (SpO2), and cerebral (CTO) and quadriceps muscle tissue oxygenation (QMTO) were measured. RESULTS During the final 15 s of ramp exercising with FiO2 0.50, Wmax (mean ± SD 270 ± 80 W), SpO2 (99 ± 1%), and CTO (67 ± 9%) were higher and the Borg CR10 Scale dyspnea score was lower (4.8 ± 2.2) than the corresponding values with FiO2 0.21 (Wmax 257 ± 76 W, SpO2 96 ± 3%, CTO 61 ± 9%, and Borg CR10 Scale dyspnea score 5.7 ± 2.6, $p < 0.05$, all comparisons). In constant-load exercising with FiO2 0.50, endurance was longer than with FiO2 0.21 (16 min 22 s ± 7 min 39 s vs. 10 min 47 s ± 5 min 58 s). With FiO2 0.50, SpO2 (99 ± 0%) and QMTO (69 ± 8%) were higher than the corresponding isotime values to end-exercise with FiO2 0.21 (SpO2 96 ± 4%, QMTO 66 ± 9%), while minute ventilation was lower in hyperoxia (82 ± 18 vs. 93 ± 23 L/min, $p < 0.05$, all comparisons). CONCLUSION In healthy subjects, hyperoxia increased maximal power output and endurance. It improved arterial, cerebral, and muscle tissue oxygenation, while minute ventilation and dyspnea perception were reduced. The findings suggest that hyperoxia enhanced cycling performance through a more efficient pulmonary gas exchange and a greater availability of oxygen to muscles and the brain (cerebral motor and sensory neurons).

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Mechanisms of Improved Exercise Performance under Hyperoxia

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Cardiopulmonary exercise testing · Oxygen supplementation

Abstract
Background: The impact of hyperoxia on exercise limitation is still incompletely understood. ***Objectives:*** We investigated to which extent breathing hyperoxia enhances the exercise performance of healthy subjects and which physiologic mechanisms are involved. ***Methods:*** A total of 32 healthy volunteers (43 ± 15 years, 12 women) performed 4 bicycle exercise tests to exhaustion with ramp and constant-load protocols (at 75% of the maximal workload [W_{max}] on FiO_2 0.21) on separate occasions while breathing ambient (FiO_2 0.21) or oxygen-enriched air (FiO_2 0.50) in a random, blinded order. Workload, endurance, gas exchange, pulse oximetry (SpO_2), and cerebral (CTO) and quadriceps muscle tissue oxygenation (QMTO) were measured. ***Results:*** During the final 15 s of ramp exercising with FiO_2 0.50, W_{max} (mean ± SD 270 ± 80 W), SpO_2 (99 ± 1%), and CTO (67 ± 9%) were higher and the Borg CR10 Scale dyspnea score was lower (4.8 ± 2.2) than the corresponding values with FiO_2 0.21 (W_{max} 257 ± 76 W, SpO_2 96 ± 3%, CTO 61 ± 9%, and Borg CR10 Scale dyspnea score 5.7 ± 2.6, $p < 0.05$, all comparisons). In constant-load exercising with FiO_2 0.50, endurance was longer than with FiO_2 0.21 (16 min 22 s ± 7 min 39 s vs. 10 min 47 s ± 5 min 58 s). With FiO_2 0.50, SpO_2 (99 ± 0%) and QMTO (69 ± 8%) were higher than the corresponding isotime values to end-exercise with FiO_2 0.21 (SpO_2 96 ± 4%, QMTO 66 ± 9%), while minute ventilation was lower in hyperoxia (82 ± 18 vs. 93 ± 23 L/min, $p < 0.05$, all comparisons). ***Conclusion:*** In healthy subjects, hyperoxia increased maximal power output and endurance. It improved arterial, cerebral, and muscle tissue oxygenation, while minute ventilation and dyspnea perception were reduced. The findings suggest that hyperoxia enhanced cycling performance through a more efficient pulmonary gas exchange and a greater availability of oxygen to muscles and the brain (cerebral motor and sensory neurons).

Introduction

Exercise performance in humans is determined by oxygen (O_2) delivery to the muscles by the cardiorespiratory system, diffusion of O_2 from the capillaries into cells, and utilization of O_2 by skeletal muscles [1, 2]. With higher exercise intensity, any further increase in O_2 supply to

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the muscles is limited; accumulation of H^+ and inorganic phosphates at the neuromuscular junction and in muscle cells reduce contractility and induce fatigue [3, 4]. A reduced O_2 supply leads to recruitment of type II muscle fibers, which are less suitable for endurance than type I fibers and thus more prone to fatigue [5]. In addition to these peripheral mechanisms of exercise limitation, the central nervous system may also limit performance by regulating the skeletal muscle mass recruited during exercise [2]. Accordingly, reduced cerebral tissue oxygenation (CTO) during exercise was associated with cessation of motor tasks [6, 7]. Moreover, the exercise-induced decline in CTO was aggravated by hypoxia [8–10], but reduced by hyperoxia along with a better exercise capacity [11].

In the current study, we further investigated the effects of breathing O_2-enriched air (FiO_2 0.5, in the following termed "hyperoxia") on exercise performance, pulmonary gas exchange, arterial, cerebral, and muscle tissue oxygenation, and perception of dyspnea to scrutinize the mechanisms of enhanced exercise performance in hyperoxia compared to normoxia (i.e., during breathing ambient air, FiO_2 0.21). We hypothesized that hyperoxia improves exercise performance and dyspnea by promoting the availability of O_2 to muscles and the brain.

Subjects and Methods

Subjects

Healthy, nonsmoking men and women aged 18–80 years not taking any regular medication were invited to participate in this study by advertisement among hospital employees, students, and other persons known to the investigators. The study was approved by the Cantonal Ethics Board of Zurich (KEK 2012-0251), and the participants provided written informed consent.

Study Design

The participants performed 2 exhaustive ramp and 2 constant-load bicycle exercise tests under hyperoxia (FiO_2 0.5) and normoxia (FiO_2 0.21), respectively, on 4 separate occasions within 4 weeks [12]. The test sequences of hyperoxia and normoxia were randomized according to a single-blinded crossover design. Balanced randomization was achieved by letting participants draw a paper with a concealed test sequence from an envelope containing an equal number of the 4 different possible test sequences. Study recruitment started in April 2013, and the last visit of the last participant was in February 2014.

Methods

At the first visit, questionnaires about health status, fitness levels scored on a 4-point Likert scale from 0 (sedentary) to 4 (very active), and anthropometric measurements were assessed and a clinical examination and spirometry were performed. The subjects were asked to refrain from strenuous exercise 24 h before the bicycle tests and to report to the laboratory 1 h after intake of a light meal.

Ramp bicycle exercising started after 2 min of unloaded pedaling with a workload of 20 W followed by a 15–25 W/min increase to exhaustion. The ramp slope was selected according to the reported individual fitness (Likert scale score 0–1: 15 W/min; Likert scale score 2: 20 W/min; Likert scale score 3–4: 25 W/min). The aim was to achieve a test duration of 8–12 min and to prevent premature or delayed transition to anaerobic exercise that might have confounded the effect of hyperoxia. Constant-load exercising was performed at 75% of the maximal workload (W_{max}) achieved under normoxia. Maximal exercise performance in the ramp and constant-load tests was defined, respectively, as W_{max} or exercise duration (endurance) for which the subject was no longer able to maintain a cycling rate >60 rpm. Perceived dyspnea and leg discomfort at end-exercise were evaluated by the Borg CR10 scale [13].

During exercise the subjects breathed through a mouthpiece connected to a flow sensor and a 2-way low-resistance T valve (Hans Rudolph Inc., Shawnee, KS, USA; 2600 Series, medium 2-way NRBV). Inspired air was delivered by a gas-mixing device (Altitrainer NP, SMTEC, Nyon, Switzerland) providing either ambient air (normoxia, FiO_2 0.21) or oxygen-enriched air (hyperoxia, FiO_2 0.50) which was connected with a tube to the T valve. The mouthpiece with a tightly fitting spout was preferred to a mask in order to ensure leakage-free breathing of the respective gas mixture. Breath-by-breath assessment of ventilation and gas exchange, pulse oximetry, and the ECG were registered with a metabolic unit (Ergostik; Geratherm Respiratory GmbH, Geschwenda, Germany). The software of the metabolic unit was specifically adapted to measure FiO_2 during both inspiration and expiration (instead of assuming a constant FiO_2 of 0.21) and to continuously optimize synchronization of the airflow and gas concentration measurements. The flowmeter and gas analyzers were calibrated prior to each test, and the system was validated with a metabolic pump simulator [14] in order to ensure the accuracy of the measurements within limits of agreement that were well within the coefficients of repeatability for $\dot{V}E$ and $\dot{V}O_2$ reported for normal subjects [15].

The tissue content of oxygenated and deoxygenated hemoglobin (O_2Hb, HHb; in U) was continuously monitored with near-infrared spectroscopy with a sampling frequency of 1 Hz (NIRO-200NX; Hamamatsu, Japan). One optode was placed and secured with adhesive tape high on the forehead to record CTO (in %); a second optode was placed parallel to the long axis of the right thigh in mid-distance between the great trochanter and the lateral epicondyle to record quadriceps muscle tissue oxygen saturation (QMTO; in %) [6]. The O_2Hb and HHb contents measured within the near-infrared spectroscopy sampling volume were normalized to express changes from baseline [16]. CTO (in %) was derived as $[O_2Hb]/([O_2Hb] + [HHb]) \times 100$. The total hemoglobin content (tHb; in U), the sum of the O_2Hb and HHb content, served as a surrogate for change in local blood volume.

Analysis

Physiologic variables from hyperoxia and normoxia tests were averaged over individually matched time periods and workloads. Variables recorded breath by breath were averaged over 60 s at rest and over successive time periods corresponding to deciles of per-

cent W_{max} in normoxia (i.e., 0–10% W_{max}, 11–20% W_{max}, etc., up to 100% W_{max} in normoxia). Thus, variables were compared at the respective submaximal isoloads/isotimes under hyperoxia versus normoxia. Mean values over the final 15 s of ramp exercising or 30 s of constant-load exercising, respectively, were computed as end-exercise values. Physiologic variables recorded under hyperoxia at the workload/time corresponding to end-exercise under normoxia were also computed and compared.

Data are summarized as means ± SD. Data at submaximal isoloads/isotimes and at end-exercise were compared between normoxia and hyperoxia with the Wilcoxon matched-pairs test.

Pearson correlation and linear regression were used for correlation of baseline characteristics and physiologic variables under hyperoxia and normoxia. Significance was assumed at $p < 0.05$.

Results

Subjects

A total of 32 subjects (12 females) aged 24–66 years, with 3–6 subjects in each decile of age, were included. The subjects were healthy, physically active nonsmokers with normal spirometry (Table 1). Complete data sets of 32 ramp tests and 29 constant-load tests were analyzed; 3 constant-load tests were not available for technical reasons.

Table 1. Baseline characteristics

Participants (women)	32 (12)
Age, years	43±15
Body weight, kg	69±12
Body height, cm	172±9
BMI	23.0±2.6
Arterial oxygen saturation (pulse oximetry), %	99±1
FVC, % predicted	114±15
FEV_1, % predicted	110±14
FEV_1/FVC, % predicted	104±8
Peak expiratory flow, % predicted	112±16
Fitness level	
0 = sedentary	0
1 = active but no regular sports activities	3
2 = 1–2 sports activities per week	7
3 = 3 sports activities per week	14
4 = >3 sports activities per week	8

Values are presented as mean ± SD or total number. FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 s.

Maximal Ramp Exercise under Hyperoxia and Normoxia

Table 2 and the Figure 1 summarize the results of the maximal ramp exercise tests. W_{max} was higher under hyperoxia than under normoxia (270 ± 80 vs. 257 ± 76 W, corresponding to an increase of 13 W [95% CI 8–19], $p < 0.001$; Table 2), although the subjects felt less dyspneic, while perception of leg fatigue was similar to that under normoxia. The O_2 uptake ($\dot{V}O_2$) at the corresponding workloads (isoloads) and at $\dot{V}O_{2\ max}$ were higher under hyperoxia than under normoxia. At loads of 40–100% W_{max} (normoxia), hyperoxia was associated with higher peripheral oxygen saturation (SpO_2) and a lower heart rate and minute ventilation ($\dot{V}E$) compared to normoxia. The reduction in $\dot{V}E$ was related to a lower breath rate, whereas the tidal volume was unchanged. Correspondingly, the ventilatory equivalents for O_2 and CO_2 at the isoloads were lower with hyperoxia than with normoxia. Compared to normoxia, CTO was higher under hyperoxia over the range of 20–100% W_{max} (normoxia), and the decline in CTO from rest to end-exercise was not only smaller but also delayed (Fig. 1). Cerebral tHb, a surrogate for regional blood volume, decreased with increasing workload under hyperoxia and normoxia. QMTO was similar under hyperoxia and normoxia at low exercise levels, and it decreased progressively with exercise (Fig. 1).

The increase in W_{max} under hyperoxia correlated with the relative difference in breath rate (in %) at W_{max} normoxia versus isoload hyperoxia ($R = 0.44$, $p = 0.020$). However, the increase in W_{max} under hyperoxia did not correlate with gender, age, anthropometrics, lung volumes, the amount of reported physical activity, and randomization of the test sequence in univariate analysis.

Constant-Load Exercise under Hyperoxia and Normoxia

Constant-load bicycle exercising at 75% W_{max} (normoxia) corresponded to a mean work rate of 188 W (range 102–290). Endurance was considerably longer under hyperoxia than under normoxia (16 min 22 s ± 7 min 39 s vs. 10 min 47 s ± 5 min 58 s, corresponding to an increase of 47 ± 38%, $p < 0.001$; Table 3). Under hyperoxia, 27/29 subjects increased their exercise time by ≥5%, and 10/29 by 50%. Only 2 subjects did not change their exercise time by more or equal than ±5%. Perception of dyspnea and leg discomfort under air and hyperoxia did not differ at the end of the tests. With progression of exercise under hyperoxia, SpO_2 and $\dot{V}O_2$ were higher, whereas the heart rate as well as $\dot{V}E$ and the breath rate were lower, resulting in lower ventilatory equivalents for O_2 and CO_2 compared to normoxia (Table 3). SpO_2 and QMTO were both higher under hyperoxia at isotime and end-exercise, whereas CTO was not significantly different but showed

Table 2. Maximal ramp bicycle exercise under normoxia and hyperoxia

	Normoxia	Hyperoxia	
	end-exercise	isoload end-exercise normoxia	end-exercise
Workload, W	257±76	257±76	270±80**
Workload, % predicted	126±27	NA	133±28**
Anaerobic threshold, W	127±41	NA	160±58**
Heart rate, bpm	171±17	164±17**	172±17
Heart rate reserve, bpm	8±10	14±10**	6±11
Tidal volume, L	2.6±0.5	2.8±0.5*	2.7±0.5
Breath rate, *n*/min	42±10	33±10**	41±10
Minute ventilation ($\dot{V}E$), L/min	106±32	90±32**	108±33
Breathing reserve, L/min	47±28	63±29**	45±29
Breathing reserve, % MVV	30±16	41±15**	29±16
Oxygen uptake ($\dot{V}O_2$), L/min	3.0±0.9	3.3±0.9**	3.6±1.0**
$\dot{V}O_2$, mL/min/kg	43±11	47±11**	53±12**
CO_2 output ($\dot{V}CO_2$), L/min	3.5±1.1	3.3±1.0	3.7±1.1*
Respiratory exchange ratio	1.2±0.1	1.0±0.1**	1.0±0.1**
$\dot{V}E/\dot{V}O_2$	36±5	27±5**	31±6**
$\dot{V}E/\dot{V}CO_2$	30±4	26±3**	29±5
O_2 pulse, mL/beat	17±4	20±5**	21±5**
End-tidal PO_2, mm Hg	110±4	315±33**	318±31**
End-tidal PCO_2, mm Hg	38±4	43±4**	39±4**
Pulse oximetry (SpO_2), %	96±3	99±0.5**	99±0.5**
Cerebral tissue SO_2 (CTO), %	61±9	69±9**	67±9*
Quadriceps muscle tissue SO_2 (QMTO), %	65±8	67±7	67±7
Cerebral total hemoglobin, U	48±17	46±22	46±22
Quadriceps total hemoglobin, U	40±13	39±12	39±13
CTO desaturation, %	6±8	0.4±6**	2±7*
QMTO desaturation, %	8±7	7±5	6±7
Borg CR10 scale dyspnea score	5.7±2.6	NA	4.8±2.2*
Borg CR10 scale leg discomfort score	6.0±2.1	NA	6.1±2.4

Values are presented as mean ± SD (n = 32). Individual values were averaged over 15 s; for isoload under hyperoxia, data from the same 15 s (isotime) as those at end-exercise under normoxia are reported. * $p < 0.05$, ** $p < 0.01$ for the comparison hyperoxia vs. end-exercise normoxia. MVV, maximal voluntary ventilation computed as 37.5 × FEV_1; U, relative units.

a significantly smaller drop over the course of exercise under hyperoxia.

The increase in endurance with hyperoxia was correlated with the reduction in breath rate (R = 0.452, p = 0.016) and the QMTO desaturation from rest to end-exercise (R = –0.389 and 0.31 under air and hyperoxia, p = 0.050 and p = 0.031).

Discussion

In this study of healthy men and women of a broad age range, we have shown that breathing oxygen-enriched air (FiO_2 0.50, hyperoxia) increases both W_{max} in progressive ramp exercising and endurance in constant-load bicycle exercising when compared to breathing ambient air (FiO_2 0.21, normoxia). The increase in submaximal load endurance of 47% was substantial and exceeded the increase in W_{max} of 5% by a factor of 10. The mechanisms of improved exercise performance with hyperoxia compared to normoxia include (1) an enhanced pulmonary gas exchange as reflected in reduced ventilatory equivalents for O_2 and CO_2, (2) an improved systemic O_2 delivery as suggested by the higher SpO_2, O_2 pulse, and $\dot{V}O_2$, and (3) higher CTO at isotime/isoload with a delayed fall near maximal exercise indicating that improved O_2 availability to cerebral motor and sensory neurons may have promoted a sustained activation of motor units and a re-

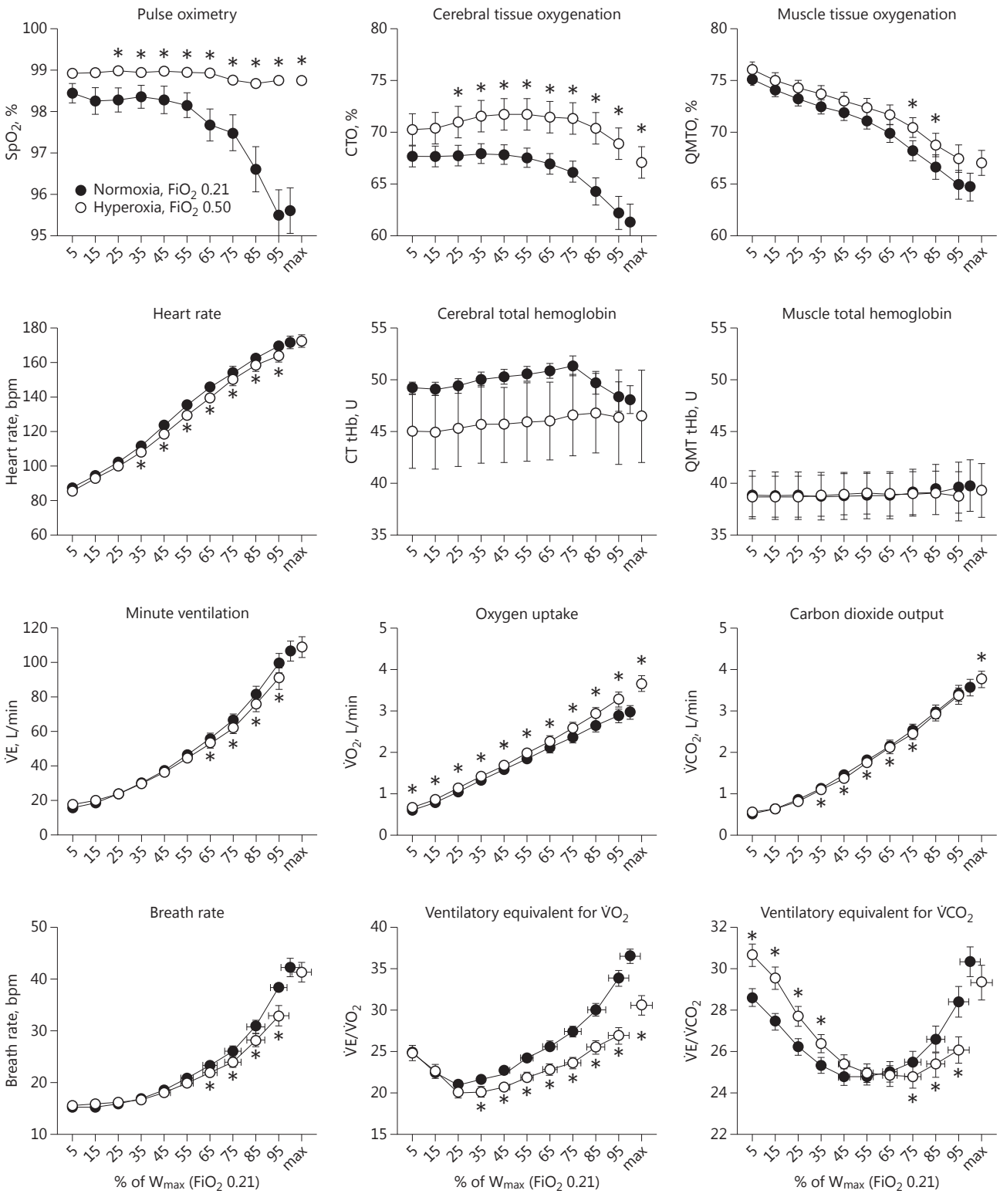

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Table 3. Constant-load bicycle exercise (at 75% W_{max} in normoxia) under normoxia and hyperoxia

	Normoxia	Hyperoxia	
	end-exercise	isotime end-exercise normoxia	end-exercise
Endurance	10 min 47 s ± 5 min 58 s	10 min 47 s ± 5 min 58 s	16 min 22 s ± 7 min 39 s**
Workload, W		184±28	184±28
Heart rate, bpm	169±17	166±14*	171±15
Heart rate reserve, bpm	7±12	10±11*	5±12
Tidal volume, L	2.5±0.5	2.5±0.5	2.5±0.5
Breath rate, *n*/min	38±9	33±8**	37±9*
Minute ventilation ($\dot{V}E$), L/min	93±23	82±18**	88±21*
Breathing reserve, L/min	25±13	33±12**	28±14
Oxygen uptake ($\dot{V}O_2$), L/min	2.8±0.8	3.0±0.8**	3.0±0.9**
$\dot{V}O_2$, mL/min/kg	40±9	44±10**	45±11**
CO_2 output ($\dot{V}CO_2$), L/min	2.9±0.8	2.8±0.7	2.8±0.8
$\dot{V}E/\dot{V}O_2$	33±5	27±5**	29±6**
$\dot{V}E/\dot{V}CO_2$	32±4	29±4**	31±4*
O_2 pulse, mL/beat	16.3±4	18±4.4**	18±5**
End-tidal PO_2, mm Hg	109±5	316±29**	319±30**
End-tidal PCO_2, mm Hg	35±5	39±5**	36±5*
Pulse oximetry (SpO_2), %	96±4	99±0**	99±1**
Cerebral tissue SO_2 (CTO), %	62±13	68±12	67±13
Quadriceps muscle tissue SO_2 (QMTO), %	66±9	69±8**	69±9**
Cerebral total hemoglobin, U	50±33	51±33	52±37
Quadriceps total hemoglobin, U	40±13	40±13	40±14
CTO desaturation, %	7±9	2±9**	2±9**
QMTO desaturation, %	6±6	4±5*	4±6
Borg CR10 scale dyspnea score	5.2±2.6	NA	4.9±2.6
Borg CR10 scale leg discomfort score	6.7±2.1	NA	6.6±2.3

Values are presented as mean ± SD (n = 29). Individual values were averaged over 30 s; isotime values under hyperoxia were averaged over the same 30 s as those at end-exercise under normoxia. * $p < 0.05$, ** $p < 0.01$ for the comparison hyperoxia vs. end-exercise normoxia. U, relative units.

duced dyspnea perception beyond the maximal exercise intensities achieved in normoxia.

The modest increase in W_{max} under hyperoxia found in the current study is in line with previous studies performed mostly in young athletes breathing oxygen-enriched air with various fractions of O_2 of 0.3–1.0 [11, 17–21]. Our data extend these findings by showing a similar effect of hyperoxia on exercise performance in nonathletic – albeit relatively fit – subjects of both genders and of a broad age range (24–66 years). The increase in W_{max} of 5% with hyperoxia was associated with a relatively greater increase in $\dot{V}O_{2\,max}$ of 24% and higher submaximal $\dot{V}O_2$ compared to normoxia, suggesting reduced external work efficiency with hyperoxia. Changes in substrate utilization, alterations in $\dot{V}O_2$ kinetics, and differences in muscle fiber type recruitment [21–23], as well as redistribution of cardiac output away from muscles and changes in $\dot{V}O_2$ of non-work-performing territories are potential explanations of these findings [19, 24].

With hyperoxia, the breath rate and $\dot{V}E$ were reduced, while $PetCO_2$, $\dot{V}CO_2$, and $\dot{V}O_2$ were increased, reflecting

Fig. 1. Synopsis of physiologic changes during progressive ramp exercising. The values represent means (±SE) over successive deciles of the maximal workload (W_{max}) achieved under normoxia for tests under normoxia and hyperoxia; i.e., the value of 5 (*x* axis) represents the mean over the range of 1–10% of W_{max} normoxia, 15 represents the mean over the range of 11–20% of W_{max} normoxia, etc. The last values represent the mean values over the final 15 s of maximal exercise. The SE for time and workloads, respectively, are shown in the lowest panels only, as they are identical for all panels. * $p < 0.05$ for comparison hyperoxia (FiO_2 0.50) vs. normoxia (FiO_2 0.21).

the greater efficiency of pulmonary gas exchange that helped to improve exercise performance. The higher $PetCO_2$ (surrogate for $PaCO_2$) that contributed to a decreased $\dot{V}E/\dot{V}CO_2$ might indicate a reduction in chemoreceptor sensitivity to CO_2 with hyperoxia [25]. The delay in the anaerobic threshold and respiratory compensation point under hyperoxia in our study support a higher cellular respiratory rate by additional glycogen oxidation and postponed anaerobic metabolism in working muscles [19]. As we did not measure blood gases in the current, healthy collective, it is uncertain whether changes in arteriovenous oxygen content difference contributed to the enhanced exercise performance under hyperoxia. Consistent with a reduced sympathetic excitation under hyperoxia [26], the heart rate was lower compared to normoxia at isoload exercise intensities, allowing for a further increase in heart rate and O_2 delivery beyond W_{max} in normoxia.

In our study, the SpO_2 decreased by 3% from rest to end-exercise under normoxia, whereas SpO_2 was maintained at 99% under hyperoxia. By enhancing systemic O_2 delivery, higher SpO_2 improvements in CTO were achieved. We assessed CTO at the prefrontal cortex due to easy accessibility, and since it has been suggested that deoxygenation of this brain region contributes to exercise limitation [7, 27–29]. Although the prefrontal cortex is not directly involved in the neuronal control of movements, it is responsible for movement planning, pacing strategies, and decision-making [30, 31]. Rasmussen et al. [32] showed that decreased frontal cortical oxygenation was associated with reduced muscle force-generating capacity. We observed that CTO was higher under hyperoxia than under normoxia at the isoloads and that the decline in CTO towards end-exercise was smaller and occurred at higher workloads, promoting greater O_2 availability to the brain with hyperoxia.

Under normoxia, cerebral tHb, a surrogate for regional cerebral blood volume, rapidly declined from 80% of W_{max} to end-exercise. The fall in cerebral tHb occurred after the nadir of $\dot{V}E/\dot{V}CO_2$ and peak $PetCO_2$, and thus might reflect cerebral vasoconstriction due to hypocapnia at exercise intensities above the anaerobic threshold [33, 34]. Under hyperoxia, a similar drop in cerebral tHb was not seen, possibly due to the delayed anaerobic threshold along with the relatively higher $PaCO_2$. These findings support the notion that in normoxia, reduced cerebral O_2 availability contributes to termination of exercising via reduced neural muscle activation [11], while hyperoxia improves exercise performance by increasing CTO. Since hyperoxia diminished the perception of dyspnea at maximal exercise despite a $\dot{V}E$ similar to that in normoxia (Table 2), we propose that the greater availability of O_2 to both sensory and motor neurons plays a role in enhancing exercise performance with hyperoxia [35–37].

In contrast to CTO, QMTO steadily declined from rest to end-exercise under both conditions, even if QMTO was slightly higher under hyperoxia. Muscle tHb levels remained unchanged over the course of exercising in normoxia and hyperoxia, indicating a stable blood flow to the muscles. These results are in line with previous reports that showed that muscle vasomotor response to exercise was not significantly influenced by hyperoxia [11, 38].

The considerably increased endurance in constant-load exercising under hyperoxia found in our study is consistent with some previous reports showing that exercise duration correlated with FiO_2 [36, 39–41]. The patterns of change in physiologic variables during constant-load exercising under hyperoxia versus normoxia were similar but not quite identical to those during maximal exercising (Table 3). Consistent with the findings on ramp exercising, $\dot{V}O_2$ was higher under hyperoxia at isotimes to normoxia, but $\dot{V}O_2$ did not further increase to end-exercise, indicating that a steady state was achieved. The lower $\dot{V}E$, together with a higher $PetCO_2$ and a reduced $\dot{V}E/\dot{V}CO_2$ under hyperoxia, also reflected an improved efficiency of pulmonary gas exchange that might have contributed to the enhanced exercise performance. In addition, the heart rate was lower under hyperoxia at isotime to normoxia, leaving a heart rate reserve that allowed for continued exercising as in the ramp tests. Hyperoxia increased SpO_2 and CTO at end-exercise with hyperoxia, and particularly prevented the fall in CTO and QMTO that occurred at end-exercise in normoxia, indicating that both cerebral and muscle tissue deoxygenation might have limited exercise performance. Unlike during maximal exercising, cerebral tHb, the surrogate for blood volume, increased from rest to the end of submaximal-load exercising under hyperoxia. Thus, submaximal-load exercising under normoxia and hyperoxia might not have been associated with a similarly severe metabolic acidosis due to lactate production, and, therefore, consecutive hyperventilation with cerebral vasoconstriction was avoided.

The current findings of a substantially improved exercise performance under hyperoxia may have clinical implications for patients suffering from conditions associated with oxygen desaturation during exercise, such as obstructive or restrictive pulmonary diseases or cardiovascular diseases including pulmonary hypertension. Our data suggest that such patients might benefit from

supplemental oxygen during daily activities or training, allowing them to achieve a greater performance with less dyspnea through improvements in pulmonary gas exchange efficiency, reduced sympathetic tone, and better oxygenation of the brain and muscles. In athletes, the use of supplemental oxygen might facilitate high-intensity training of specific muscle groups.

Conclusions

This study shows that hyperoxia improves exercise performance during both progressive ramp and constant-load bicycle exercising in a collective including healthy men and women of a broad age range and varying fitness levels. The improvement in exercise performance was related to a higher efficiency of pulmonary gas exchange, a reduced ventilatory work and heart rate at isoloads, and increased SpO_2, CTO, and QMTO. Together with the reduced perception of dyspnea during hyperoxia, these findings suggest that exercise limitation is related to cardiopulmonary as well as muscular and central nervous system mechanisms. The data may help to better understand the mechanisms of exercise limitation in normoxia and to guide training and rehabilitation including the use of O_2 supplementation in patients with cardiorespiratory impairment.

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Financial Disclosure and Conflicts of Interest

None of the authors has any conflict of interest regarding the present work.

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